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TRANSMITTAL LETTER

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1. English translation of priority document Japanese Patent Application No. 322874/1998; and
2. Return Post Card

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Patent Application No. 322874/1998

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【Title of the Invention】
Bone—pathobolism Treating Agent

【Number of claims】 3

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【Name of Submission】 Specification 1

【Name of Submission】 Drawings 1

【Name of Submission】 Abstract 1

【Document Name】 Specification

【Title of the Invention】 BONE-PATHOBOLISM TREATING AGENT

【Claims】

【Claim 1】 A bone-pathobolism treating agent comprising at least one substance selected from the group consisting of osteoclastogenesis inhibitory factor (OCIF), its homologs, and its variants and a polysaccharide or its derivatives.

【Claim 2】 The bone-pathobolism treating agent according to claim 1, wherein the polysaccharide or its derivatives is heparin or dextran sulfate.

【Claim 3】 A method for enhancing the activity of osteoclastogenesis inhibitory factor (OCIF) comprising using a polysaccharide or its derivatives.

【Detailed Description of the Invention】

【0001】

【Technical Field where the Invention Belongs】

The present invention relates to a novel bone-pathobolism treating agent having high activity and high persistence. The bone-pathobolism treating agent of the present invention has excellent therapeutic activity against bone-pathobolism such as osteoporosis, hypercalcemia, or chronic articular rheumatism and is useful as a medicine.

【0002】

【Background Art】

Bones not only have an ability of supporting the body but also function as the largest storage-organ of calcium in the organism and 99% of the calcium present in the organism is accumulated in the bones. In addition, bones are always remodelled through opposite actions of bone resorption and bone formation (osteogenesis). This

【Document Name】 Specification

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【0002】

【Background Art】

Bones not only have an ability of supporting the body but also function as the largest storage-organ of calcium in the organism and 99% of the calcium present in the organism is accumulated in the bones. In addition, bones are always remodelled through opposite actions of bone resorption and bone formation (osteogenesis). This

plays an important role on the maintenance of homeostasis of serum calcium. It is known that the activation of osteoclasts which play an important role in bone resorption causes excessive flow of calcium into blood from bones to break the homeostasis of calcium in blood and induces hypercalcemia. Hypercalcemia is a disease which occurs due to bone metastasis of cancer and the number of patients who suffer from it is expected to increase so that development of a treating agent is desired to be created in a hurry. At present, calcitonin, its derivatives, and bisphosphonate derivatives are used as such hypercalcemia treating agents. However, their therapeutic effect is not satisfactory and development of novel drugs replacing them is desired.

【0003】

On the other hand, it has been reported that osteoclastogenesis inhibitory factor (OCIF) (WO96/26217) known as a protein factor inhibiting differentiation of osteoclasts has a hypocalcemic [Biochemical and Biophysical Research Communications, Vol. 245, pp382-387 (1998); Endocrinology, Vol. 139, pp4012-4015 (1998)]. OCIF is expected as a quite new agent treating hypercalcemia. However, since it is a protein, OCIF is metabolized rapidly in the organism. Accordingly, development of an OCIF-preparation which is safer and has more enhanced action has been desired.

【0004】

【Problems to be Solved by the Invention】

Under the above circumstances, the inventors of the present invention have made extensive investigation, and as a result, they have found that the effect of OCIF against bone-pathobolism can be further increased by added a polysaccharide to OCIF to form a preparation. Therefore, problem of the present invention is to

provide a bone-pathobolism treating agent in which the effect of OCIF against bone-pathobolism has been further increased and the effect has been rendered persistent.

【0005】

【Means to Solve the Problems】

The present invention relates to a bone-pathobolism treating agent comprising at least one substance selected from the group consisting of osteoclastogenesis inhibitory factor (OCIF), its homologs and its variants, and a polysaccharide or its derivatives.

In the present invention, heparin or dextran sulfate may be preferably used as the above polysaccharideor its derivative.

According to the present invention, there is provided a therapeutic agent having excellent activity to bone-pathobolism such as osteoporosis, hypercalcemia, or chronic articular rheumatism and persistence of the activity. The therapeutic agent is useful as a medicine.

The present invention also relates to a method for enhancing the activity of osteoclastogenesis inhibitory factor by using a polysaccharide or its derivatives.

【0006】

【Embodiments of the Invention】

The present invention relates to a bone-pathobolism treating agent comprising at least one substance selected from the group consisting of osteoclastogenesis inhibitory factor (OCIF), its homologs and its variants, and a polysaccharide or its derivatives.

【0007】

OCIF used in the present invention is natural type or recombinant type obtained by the method described in WO96/26217. Though its origin is not particularly limited, specifically

preferred OCIF is human type.

In the present invention, homologs and variants of OCIF may be used. The homologs include those obtained by preparing a cDNA library from IMR-90 cell (ATCC CCL-186) by using poly $(A)^+$ RNA, obtaining cDNA of OCIF homolog by a hybridization method using OCIF cDNA fragment as a probe, inserting the cDNA into an expression vector, introducing the vector into a usually used host, expressing the cDNA in the host, and purifying by a conventional method. More specifically, the homologs include OCIF2, OCIF3, OCIF4, and OCIF5 as described in WO96/26217.

【0008】

The variants include those in which one or more amino acids have been inserted in, added to, substituted in, or deleted from the amino acid sequence of OCIF. More specifically, the variants include those obtained by preparing OCIF variant cDNA by introducing substitutent or deletion mutant into OCIF cDNA by a PCR method or cleavage with a restriction enzyme, inserting the cDNA into an expression vector, incorporating the vector into a usually used host, expressing the cDNA in the host, and purifying by a conventional method.

【0009】

The polysaccharide used in the present invention is a polymer (glucan) formed through glycoside bonding of monosaccarides, preferably a heteropolysaccharide (heteroglycan) having 2 or more constituent monosaccharides. More specifically, the polysaccharide which can be used include natural polysaccharides such as hyaluronic acid, chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, carrageenan, pectin, or heparin, synthetic polysaccharides such as dextran, and synthetic polysaccharide

derivatives such as dextran sulfate. Among those, sulfate ester of glucan is particularly preferably used. For example, heparin having a molecular weight of 3,000 to 6,000 or dextran sulfate having a molecular weight of 5,000 to 10,000 is used.

【0010】

The bone-pathobolism treating agent of the present invention is preferably a combination of at least one substance selected from the group consisting of OCIF, its homologs and its variants and a polysaccharide or its derivatives in a proportion of 1 to 100 folds, particularly 1 to 16 folds of the polysaccharide and its derivatives as a basis of the amount of the OCIF, its derivatives and variants. The preparation of the present invention comprising a combination of at least one substance selected from the group consisting of OCIF, its analogs, and its variants and a polysaccharide or its derivatives is useful as a bone-pathobolism treating agent having excellent persistence and therapeutic effect as compared with administration of OCIF alone and is effective against bone-pathobolisms such as osteoporosis, hypercalcemia, chronic articular rheumatism.

【0011】

The preparation of the present invention is safely administered orally or parenterally to humans or animals as a medicine. Parenteral administration includes intravenous injection, intramuscular injection, hypodermic injection, nasal administration, intraoral administration, permucomembraneous administration, etc. The preparations to be administered by these administration routes can be formulated together with pharmacologically acceptable vehicles, excipients, lubricants, colorants, etc. as a medical composition in accordance with a known pharmaceutical production method. When

an injection agent is prepared, OCIF and a polysaccharide, optionally a pH adjuster, a buffer, a stabilizer, a solubilizer, etc. are added to form injection agent by a conventional method. In this case, known additives such as human serum albumin and a surfactant may be used in combination. As the surfactant, polyanions and anionic surfactants are contained. The injection agent can be dispensed in vials to form a solution agent or prepared as a freeze-dried agent which upon use is dissolved in distilled water, physiological saline or the like at appropriate timing.

Upon administering OCIF to normal rats once a day for continuous 2 weeks in a dose of 3 or 24 mg/kg·day, increases in bone density and amount were observed, but neither histopathological disorder nor change in number of hemocyte was observed in 38 tissues (H. Yasuda et al.: Endocrinology, Vol. 139, pp1329-1337 (1998)). Thus, the action of OCIF is highly specific to bone and it is expected that OCIF can be administered safely to humans.

【0012】

The amount and method of administration of the bone-pathobolism treating agent of the present invention to patients are not limited particularly, since they may vary depending on the severity of symptom, age, health condition, and weight of the patient. For example, the agent may be parenterally administered once to several times a day in a dose of about 0.01 to 1 mg/kg per day for adults. The activity of the preparation of the present invention can be determined by measuring the concentration of serum calcium. For example, OCIF solution prepared with a suitable solvent and being added a polysaccharide is intravenously administered to a rat, blood is then collected at each time scheduled, and the calcium concentration in the serum is measured by a conventional method.

【0013】

The present invention also relates to a method for enhancing the activity of osteoclastogenesis inhibitory factor by use of a polysaccharide or its derivatives. According to the present invention, the concentration of OCIF in blood can be increased to enhance the action of OCIF lowering the serum calcium level.

【0014】

【Example】

The following examples are presented in order to more specifically explain the present invention by the examples. However, they are only illustrations and the present invention should not be limited thereby at all.

【0015】

【Example 1】

Production of Injection Agent - 1

500 μg of human OCIF obtained by the method described in WO96/26217 and 2 mg of heparin were dissolved in 5 ml of 10 mM sodium phosphate buffer solution (pH 7.0) containing 0.15 M NaCl and 0.01% Tween 80, and the resulting solution was sterilized by passing through a 0.22 μm sterile filter (Millex GV, Millipore Co.), and then packed in a vial to obtain intravenous injection agent.

【0016】

Production of Injection Agent - 2

500 μg of human OCIF obtained by the method described in WO96/26217 and 2 mg of dextran sulfate were dissolved in 5 ml of 10 mM sodium phosphate buffer solution (pH 7.0) containing 0.15 M NaCl and 0.01% Tween 80, and the resulting solution was sterilized by passing through a 0.22 μm sterile filter (Millex GV, Millipore Co.), and then packed in a vial to obtain injection agent for

intravenous injection.

【0017】

【Example 2】

Effect of OCIF Lowering Calcium Concentration in Serum by the Addition of a Polysaccharide

To 2 ml of 0.25 mg/ml human OCIF solution prepared by dissolving human OCIF (dimer type) (genetic recombinant type OCIF obtained by the method described in WO96/26217) in 10 mM sodium phosphate buffer solution (pH 7.0) (hereafter, referred to as a solvent) containing 0.15 M NaCl and 0.01% Tween 80, 2 mg of dextran sulfate (molecular weight 8,000 or 10,000: Sigma AB, and molecular weight 5,000 or 50,000: Wako Pure Chemical Industry Co., Ltd.), or heparin (207.8 or 171.2 unit/mg: Wako Pure Chemical Industry Co., Ltd. and molecular weight 3,000 or 6,000: Sigma AB) was dissolved and then the solution was kept at 4°C for a day. At the same time, 0.25 and 2.5 mg/ml human type OCIF solutions and the solvent were also kept at 4°C for a day similarly. Using these sample solutions to be tested, OCIF and dextran sulfate administered group (D group), OCIF and heparin administered group (H group) (D group and H group were administered with 0.5 mg/kg OCIF, respectively), OCIF alone administered group (administered with 0.5 mg/kg and 5 mg/kg OCIF, respectively), and solvent administered group were provided. Four weeks age female Wistar rats were once intravenously administered with the samples at a dose of 2 ml/kg. After 3 hours from the administration, blood was collected from the eyehole to prepare serum. The calcium level in the obtained serum was measured using Calcium C Test (Wako Pure Chemical Industry Co., Ltd.). Figure 1 shows the results. As a result, it was observed that the administration of 0.5 mg/kg of human OCIF to which one of various dextran sulfates

or heparin has been added exhibited a significant enhancing effect in hypocalcemic action. Therefore, it was confirmed that the addition of a polysaccharide can enhance hypocalcemic action of human OCIF.

【0018】

【Example 3】

Enhancing Effect of the OCIF-action by the amount of added polysaccharide

Dextran sulfate (molecular weight 5,000: Wako Pure Chemical Industry Co., Ltd.) was dissolved in 2 ml of the 0.25 mg/ml human OCIF solutions prepared in the same manner as in Example 2, in a proportion of 1, 2, 4, 8, or 16 folds by weight, based on the amount of OCIF, respectively, and the mixtures were kept at 4°C for a day. Similarly, heparin (207.8 units/mg: Wako Pure Chemical Industry Co., Ltd.) was dissolved in 2ml of 0.25 mg/ml human OCIF solutions in the same proportion and the mixtures were kept at 4°C for a day.

Further, 4 mg/ml dextran sulfate or heparin solution, 0.25 and 2.5 mg/ml human OCIF solutions, and the solvent alone were similarly kept at 4°C for a day, respectively. These test sample solutions were once intravenously administered to four weeks age female Wistar rats at a dose of 2 ml/kg. After 3 hours from the administration, blood was collected from the eyehole to prepare serum. The calcium level in the obtained serum was measured using Calcium C Test (Wako Pure Chemical Industry Co., Ltd.). Figure 2 shows the results. As a result, significant hypocalcemic action was recognized when dextran sulfate was added 4 folds or more in a basis on human OCIF. Significant hypocalcemic action was also seen when an amount of heparin equivalent to human OCIF was added. Therefore, it was confirmed that the hypocalcemic action of OCIF can further enhance by simultaneously administrating human OCIF

and a polysaccharide in specific proportion.

【0019】

【Example 4】

Enhancing effect on persistence of OCIF activity by the addition of polysaccharides

After dissolving 20 mg of dextran sulfate (molecular weight 5,000: Wako Pure Chemical Industry Co., Ltd.) in 2 ml of 2.5 mg/ml human OCIF solution prepared with the solvent, the mixture was kept at 4°C for a day. 20 mg heparin (207.8 units/mg: Wako Pure Chemical Industry Co., Ltd.) was also dissolved in 2 ml of the 2.5 mg/ml human OCIF solution and similarly kept at 4°C for a day. Separately, 2.5 mg/ml human OCIF solution and the solvent were also kept at 4°C for a day. Four weeks age female Wistar rats were intravenously administered with the test sample solutions at a dose of 2 ml/kg (5 mg/kg as the amount of OCIF) respectively. After 3, 6, and 9 hours from the administration, blood was collected from the eyehole to prepare serum. The calcium level in the obtained serum was measured using Calcium C Test (Wako Pure Chemical Industry Co., Ltd.). Figure 3 shows the results. As a result, though a significant decrease in serum calcium level was observed in the group administered with 5 mg/kg human OCIF solution alone after 3 hours from the administration, no significant hypocalcemic action was observed after 6 and 9 hours after the administration, respectively.

On the other hand, 2.5 mg/ml human OCIF solution to which dextran sulfate or heparin was added in amounts 4 folds of human OCIF had a significant hypocalcemic effect even after 9 hours from the administration. Therefore, it was confirmed that the simultaneous addition of human OCIF and a polysaccharide can give persistence enhancing effect.

【0020】

【Example 5】

Enhancing effect on persistence of OCIF concentration in blood by the addition of polysaccharides

1 ml of 4 mg/ml of dextran sulfate was added to 1 ml of the 1 mg/ml human OCIF solution prepared in the same manner as described in Example 2, and the obtained mixture was kept at 4°C for a day. The test sample solution was intravenously administered to 9 weeks age male Wistar rats at a dose of 1 ml/kg. After 2, 5, 10, 15, 30, 45, 60, 120, 240, 360, 480, 600, 720, and 1440 minutes from the administration, blood was collected from the eyehole to prepare serum. The human OCIF level in the obtained serum was measured by the ELISA described in WO96/26217 using monoclonal antibodies capable of recognizing dimer type OCIF, and monoclonal antibodies capable of recognizing monomer type OCIF (Biochemical and Biophysical Research Communications, Vol. 245, pp382-387 (1998)). The total OCIF level was calculated as the sum of the dimer type OCIF level and monomer type OCIF level. Figures 4 and 5 show the results. As a result, the group administered with the human OCIF solution to which dextran sulfate was added 4 folds of the human OCIF maintained evidently high OCIF level in blood as compared with the group administered with 500 μg/kg human OCIF alone (Figure 4). It was confirmed that the conversion of dimer type OCIF to monomer type OCIF in blood was inhibited (Figure 5). Therefore, the addition of a polysaccharide may persist OCIF level in blood, particularly the level of dimer type OCIF having high hypocalcemic activity (Biochemical and Biophysical Research Communications, Vol. 245, pp382-387 (1998)).

【0021】

【Effects of the Invention】

According to the present invention, there is provided a bone-pathobolism treating agent comprising at least one substance selected from the group consisting of osteoclastogenesis inhibitory factor, its homologs, and its variants and a polysaccharide or its derivatives. According to the present invention, there is provided a therapeutic agent having excellent effect on bone-pathobolism such as osteoporosis, hypercalcemia, or chronic articular rheumatism and persistence of the activity. The therapeutic agent is useful as a medicine.

【Brief Description of Drawings】

【Figure 1】

Figure 1 shows calcium concentration in serum after 3 hours from the administration of the preparation containing OCIF and added polysaccharide in Example 2.

【Explanation of symbols】

D-1: 0.5 mg/kg OCIF + 2 mg/kg dextran sulfate (molecular weight 5,000)

D-2: 0.5 mg/kg OCIF + 2 mg/kg dextran sulfate (molecular weight 8,000)

D-3: 0.5 mg/kg OCIF + 2 mg/kg dextran sulfate (molecular weight 10,000)

H-1: 0.5 mg/kg OCIF + 2 mg/kg heparin (207.8 units/mg)

H-2: 0.5 mg/kg OCIF + 2 mg/kg heparin (171.2 units/mg)

H-3: 0.5 mg/kg OCIF + 2 mg/kg heparin (molecular weight 3,000)

H-4: 0.5 mg/kg OCIF + 2 mg/kg heparin (molecular weight 6,000)

**: Significant (Significance level: p values $\leqq$ 1 %)

【Figure 2】

Figure 2 shows calcium concentration in serum after 3 hours

from the administration of the preparation containing OCIF and polysaccharide with various mixing ratios in Example 3.

【Explanation of symbols】

**: Significant (p values ≦ 1 %)

【Figure 3】

Fig ure 3 shows calcium concentration in serum after 3, 6, and 9 hours, respectively, from the administration of the preparation containing OCIF and added polysaccharide in Example 4.

【Explanation of symbols】

**: Significant (p values ≦ 1 %)

【Figure 4】

Fig ure 4 shows time-dependent change of OCIF concentration in blood when a preparation containing OCIF and added polysaccharide was administered in Example 5.

【Explanation of symbols】

A: A figure illustrating the concentration of dimer type OCIF in blood.

B: A figure illustrating the concentration of monomer type OCIF in blood.

●: OCIF

○: OCIF + dextran sulfate

【Figure 5】

Fig ure 5 shows time-dependent change in the proportion of monomer type OCIF/dimer type OCIF in blood when a preparation containing OCIF and added polysaccharide was administered in Example 5.

【Explanation of symbols】

A: OCIF

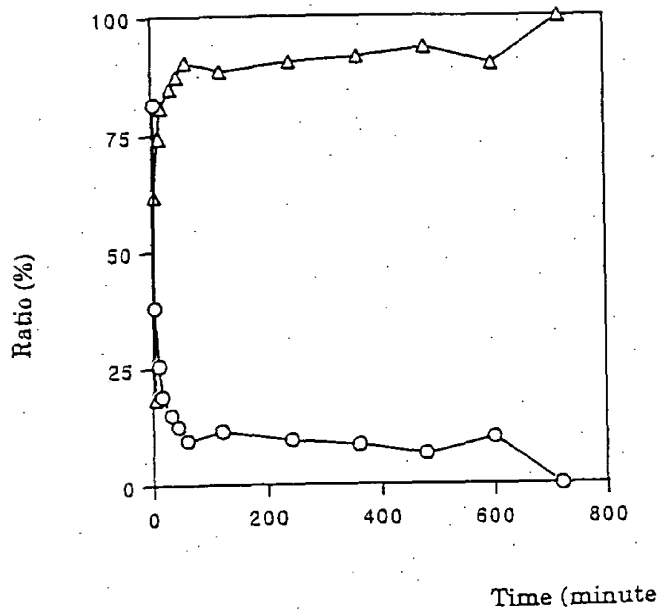
B: OCIF + dextran sulfate

○: Dimer type OCIF

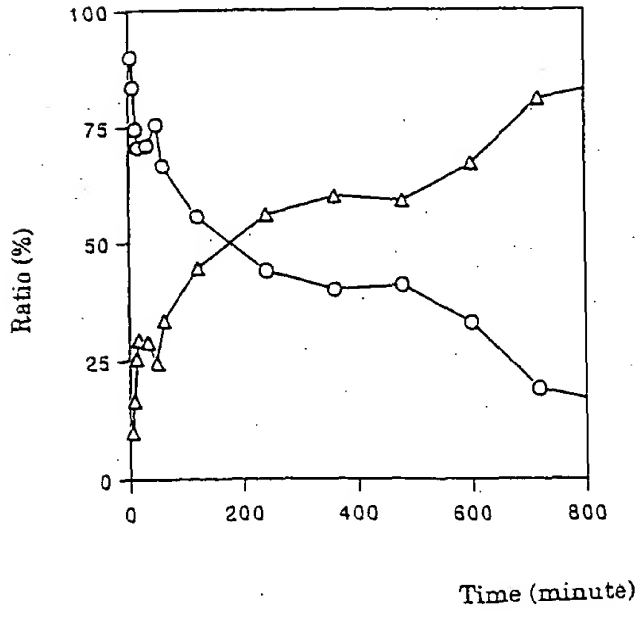
Δ: Monomer type OCIF

[Figure 5]

A

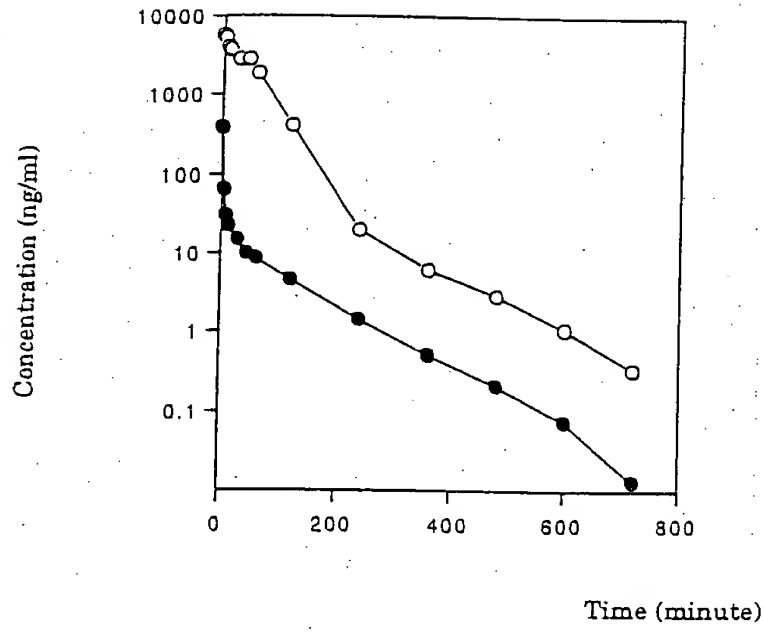

100
75
50
25
0
Ratio (%)
0
200
400
600
800
Time (minute)

B

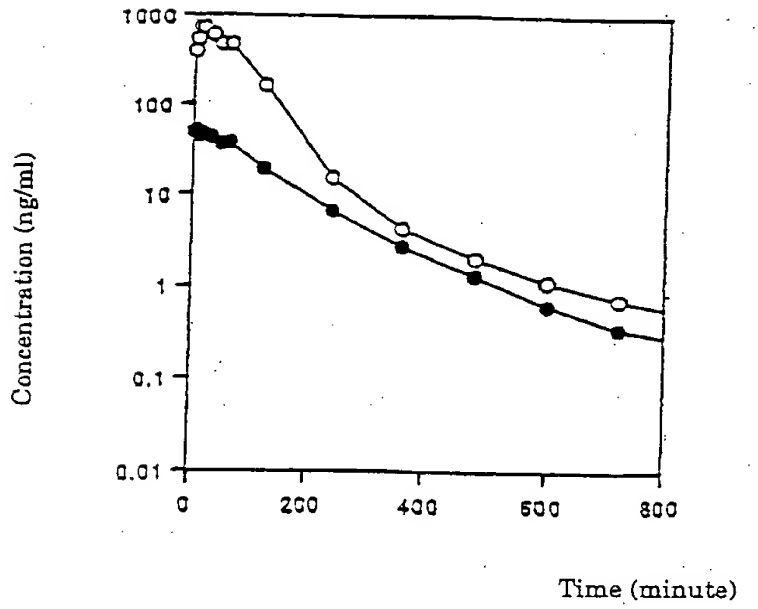

100
75
50
25
0
Ratio (%)
0
200
400
600
800
Time (minute)

[Figure 4]

A


10000
1000
100
10
1
0.1
0
200
400
600
800
Concentration (ng/ml)
Time (minute)

B


1000
100
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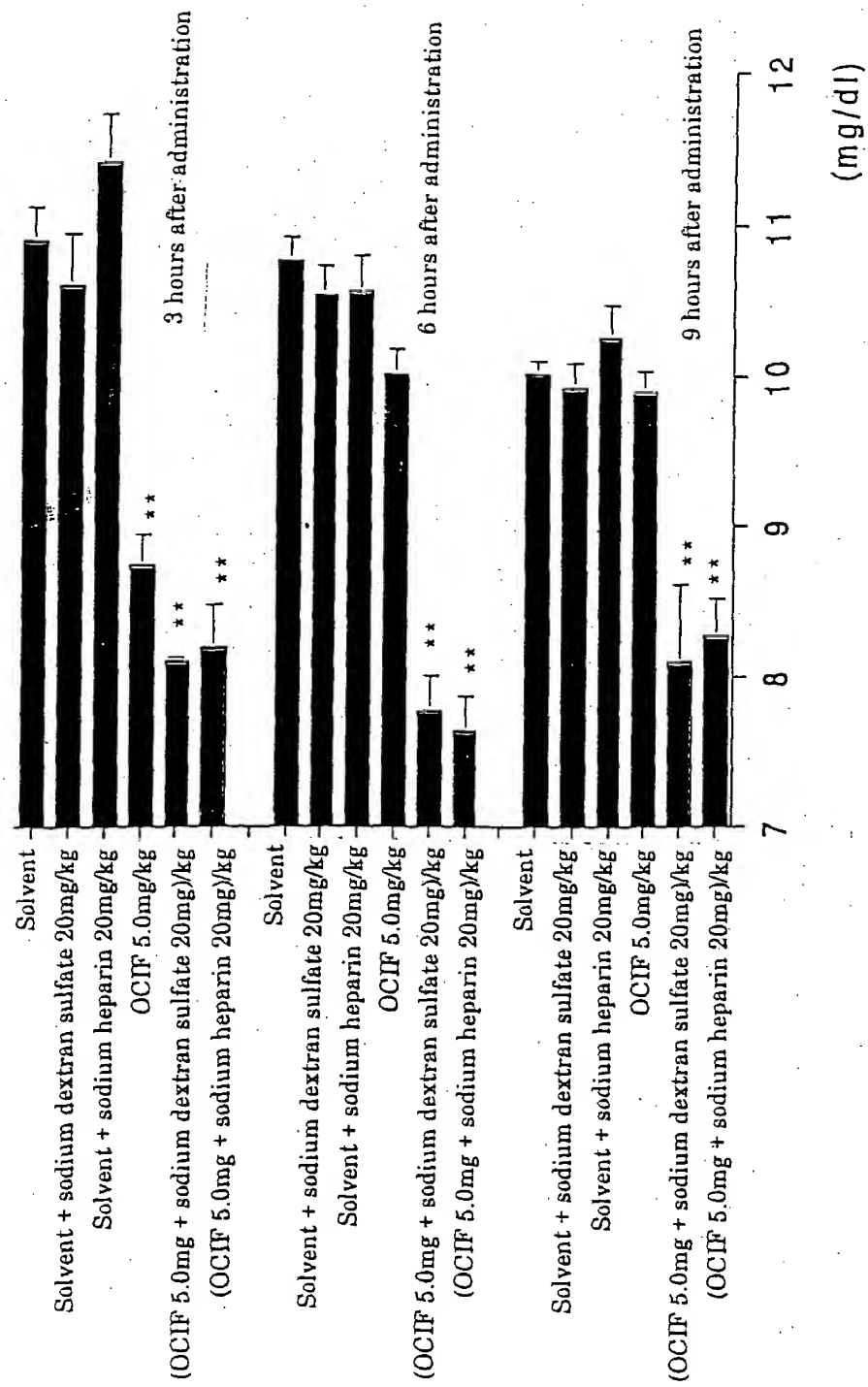
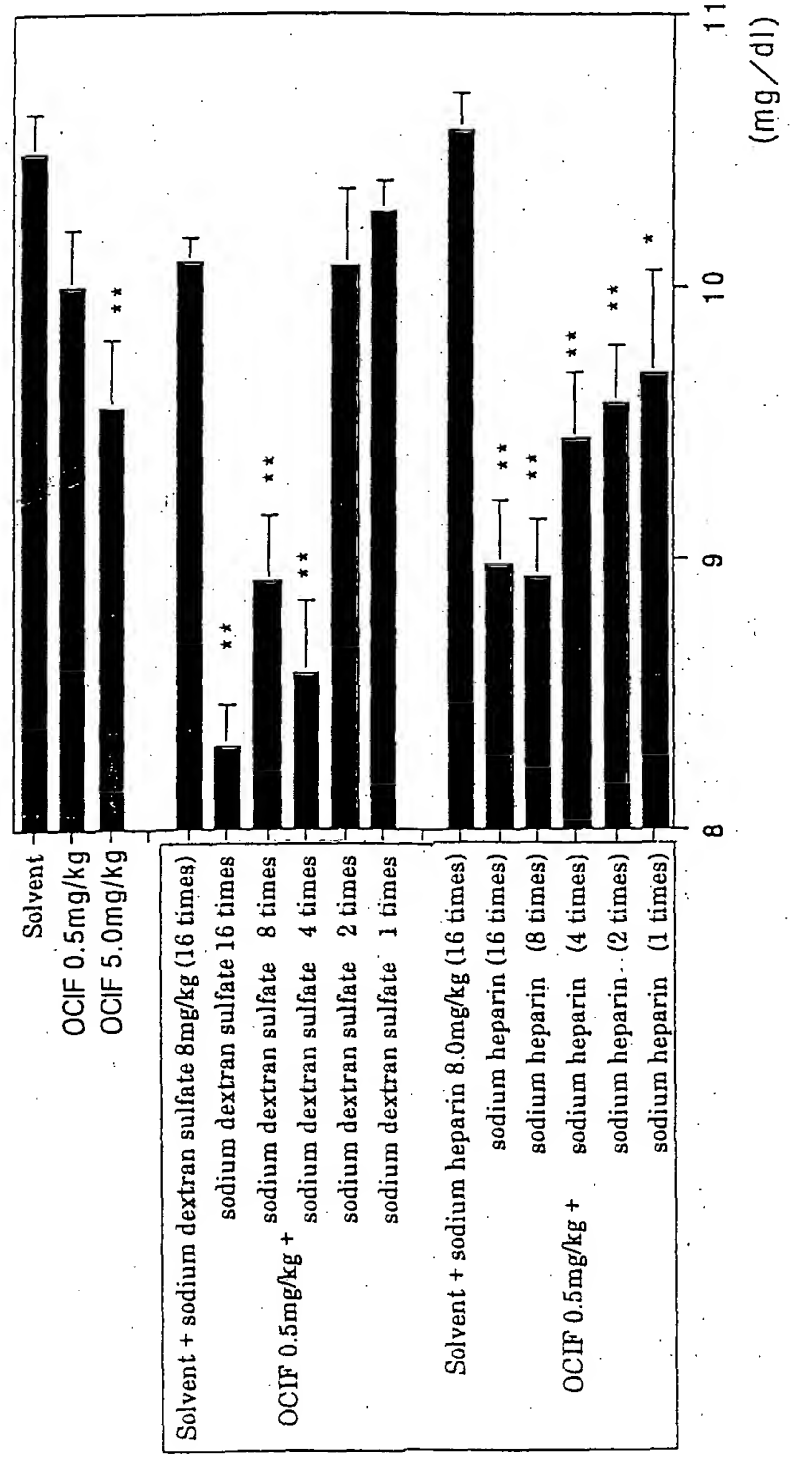
0.1
0.01
0
200
400
600
800
Concentration (ng/ml)
Time (minute)

[Figure 3]


3 hours after administration
6 hours after administration
9 hours after administration
Solvent
Solvent + sodium dextran sulfate 20mg/kg
Solvent + sodium heparin 20mg/kg
OCIF 5.0mg/kg
(OCIF 5.0mg + sodium dextran sulfate 20mg)/kg
(OCIF 5.0mg + sodium heparin 20mg)/kg
**
7
8
9
10
11
12
(mg/dl)

[Figure 2]


Solvent
OCIF 0.5mg/kg
OCIF 5.0mg/kg
Solvent + sodium dextran sulfate 8mg/kg (16 times)
sodium dextran sulfate 16 times
OCIF 0.5mg/kg + sodium dextran sulfate 8 times
sodium dextran sulfate 4 times
sodium dextran sulfate 2 times
sodium dextran sulfate 1 times
Solvent + sodium heparin 8.0mg/kg (16 times)
sodium heparin (16 times)
sodium heparin (8 times)
OCIF 0.5mg/kg + sodium heparin (4 times)
sodium heparin (2 times)
sodium heparin (1 times)
8
9
10
11
(mg/dl)
**
**
**
**
**
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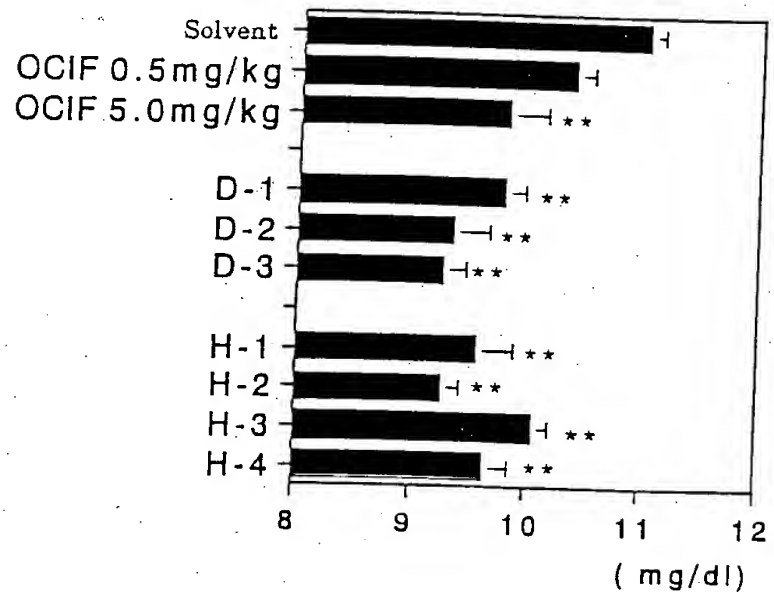
[Document Name] Drawings

[Figure 1]



【Document Name】 Abstract

【Abstract】

【Problem】 To provide a noble bone-pathobolism treating agent.

【Means to be solved】

The present invention relates to a bone-pathobolism treating agent comprising at least one substance selected from the group consisting of osteoclastogenesis inhibitory factor (OCIF), its homologs and its variants, and a polysaccharide. Dextran sulfate, heparin, etc. may be used as the above polysaccharide.

【Effect】 According to the present invention, there is provided a therapeutic agent having excellent effect on bone-pathobolism such as osteoporosis, hypercalcemia, or chronic articular rheumatism and persistence of the activity. The therapeutic agent is useful as a medicine.

【Drawing】 None